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Guidelines for Management of Idiopathic Normal Pressure Hydrocephalus (Third Edition): Endorsed by the Japanese Society of Normal Pressure Hydrocephalus

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Abstract

Among the various disorders that manifest with gait disturbance, cognitive impairment, and urinary incontinence in the elderly population, idiopathic normal pressure hydrocephalus (iNPH) is becoming of great importance. The first edition of these guidelines for management of iNPH was published in 2004, and the second edition in 2012, to provide a series of timely, evidence-based recommendations related to iNPH. Since the last edition, clinical awareness of iNPH has risen dramatically, and clinical and basic research efforts on iNPH have increased significantly. This third edition of the guidelines was made to share these ideas with the international community and to promote international research on iNPH. The revision of the guidelines was undertaken by a multidisciplinary expert working group of the Japanese Society of Normal Pressure Hydrocephalus in conjunction with the Japanese Ministry of Health, Labour and Welfare research project. This revision proposes a new classification for NPH. The category of iNPH is clearly distinguished from NPH with congenital/developmental and acquired etiologies. Additionally, the essential role of disproportionately enlarged subarachnoid-space hydrocephalus (DESH) in the imaging diagnosis and decision for further management of iNPH is discussed in this edition. We created an algorithm for diagnosis and decision for shunt management. Diagnosis by biomarkers that distinguish prognosis has been also initiated. Therefore, diagnosis and treatment of iNPH have entered a new phase. We hope that this third edition of the guidelines will help patients, their families, and healthcare professionals involved in treating iNPH.

Keywords: clinical guideline, idiopathic normal pressure hydrocephalus, diagnosis, treatment, management

CONTENTS

Abbreviation

Aβ: amyloid β protein
AC: anterior commissure
AD: Alzheimer's disease
AICs: antibiotic impregnated shunt catheters
AVIM: asymptomatic ventriculomegaly with features of iNPH on MRI
BPSD: behavioral and psychological symptoms of dementia
BVR: brain/ventricle ratio
CA: callosal angle
CAPPAH sign: convexity apparent hyperperfusion sign
CBF: cerebral blood flow
CHPV: Codman-Hakim programmable valve
Cout: CSF outflow conductance
CSF: cerebrospinal fluid
CT: computed tomography
DAT: dopamine transporter
DESH: disproportionately enlarged subarachnoid-space hydrocephalus
DTI: diffusion tensor imaging
EI: Evans Index
ETV: endoscopic third ventriculostomy
FA: fractional anisotropy
FAB: frontal assessment battery
FDG: fluorodeoxyglucose
GMC: Guidelines Management Committee
HC: head circumference
HDS-R Hasegawa's dementia scale-revised
ICP: intracranial pressure
iNPH: idiopathic normal pressure hydrocephalus
iNPHGS: iNPH grading scale
LBD: Lewy body disease
LOVA: longstanding overt ventriculomegaly in adults
LP: lumboperitoneal
LRG: leucine-rich α2-glycoprotein
MIBG: metaiodobenzylguanidine
MMSE: Mini-Mental State Examination
MRI: magnetic resonance imaging
mRS: modified Rankin Scale
NAA/Cr: N-acetylaspartate/Creatine
NFL: neurofilament light chain
NPH: normal pressure hydrocephalus
PaVM: panventriculomegaly with a wide foramen of Magendie and large cisterna magna
PC: posterior commissure
PET: positron emission tomography
PiB: Pittsburgh compound B amyloid imaging
PSP: progressive supranuclear palsy
p-tau: phosphorylated tau
PTPRQ: protein tyrosine phosphatase receptor type Q
QALY: quality-adjusted life year
RAVLT: rey auditory verbal learning test
RBMT: rivermead behavioral memory test
RCT: randomized controlled trial
RI: radio isotope
Rout: CSF outflow resistance
SINPHONI: Study of Idiopathic Normal Pressure Hydrocephalus on Neurological Improvement
sNPH: secondary normal pressure hydrocephalus
SPECT: single-photon emission computed tomography
TMT: trail making test
t-tau: total tau
TUG: timed up & go test
VA: ventriculo-atrial
VP: ventriculo-peritoneal
WAIS: Wechsler adult intelligence scale

Introduction

Geriatric medical and nursing care are important contemporary topics in Japan's rapidly aging society. One of the important health conditions that disproportionately affects the elderly is normal pressure hydrocephalus (NPH), a condition characterized by gait disturbance, cognitive impairment, and urinary incontinence.

NPH was first reported by Drs. Hakim and Adams in 1965 in a case series in which they described presentations of the triadic syndrome above, along with ventricular enlargement (ventriculomegaly) despite cerebrospinal fluid (CSF) pressure being within the normal range.[1] In all cases treated in that series, symptomatic improvement was achieved by the surgical placement of a ventriculo-atrial shunt to divert CSF.[1,2] The condition was classified into idiopathic NPH (iNPH), which is of unknown origin, and secondary NPH (sNPH), in which symptoms appear subsequent to an acquired neurological injury (e.g., subarachnoid hemorrhage or meningitis). Other categories—congenital/developmental NPH and familial NPH—include cases with congenital ventriculomegaly that remained asymptomatic until advanced age, occasionally with a familial component. sNPH is not difficult to diagnose, as it tends to follow an obvious etiological event. Differential diagnosis of iNPH, in contrast, is by no means straightforward, given its gradual onset and symptomatic progression, as well as its pathological similarity to a myriad of other diseases; moreover, the hallmarks of cognitive dysfunction, gait disturbance, and urinary incontinence are more often attributable to non-specific causes in the elderly. Affected patients are frequently misdiagnosed with Alzheimer's disease and other neurodegenerative diseases, since the neuroimaging hallmarks of iNPH are difficult to distinguish from those of cerebral atrophy in general. iNPH has long been conceptualized as a form of "treatable dementia." The undue focus of past therapeutic strategies on this aspect, and the consequent over-diagnosis of iNPH, however heralded case after case of ineffective surgeries and complications thereof, leading to that concept being neglected and no longer considered as a useful clinical definition. Moreover, iNPH is a communicating hydrocephalus, which distinguishes it from sNPH following subarachnoid hemorrhage or meningitis, and the failure of past classification schemes to regard this difference has acted as a barrier to properly understanding the condition. Neither the etiology of iNPH nor any of its pathogenetic mechanisms have been elucidated till date: half a century since its first description, the prefix "idiopathic" remains stubbornly attached. Pathological and epidemiological research have yielded valuable fundamental knowledge to facilitate the understanding of secrets of several diseases, but for iNPH, these lines of inquiry have only just begun.

Japanese Guidelines of iNPH: History and Revisions

The world's first clinical guidelines for iNPH in Japan were published in 2004, with the aim of standardizing its diagnosis and treatment and rectifying the high variability in related decisions across regions, facilities, and doctors.[3] The CSF tap test—a diagnostic test involving the drainage of CSF from the spinal canal—occupied a central dominant role within the diagnostic flowchart printed in the first edition. Clinicians' awareness of iNPH rose dramatically following the publication of the guidelines, as did the number of affected patients who were treated with CSF shunt placement; in tandem, basic and clinical researches into the condition have made tremendous strides. Recognizing the need for the global dissemination of data obtained from high-evidence-level study designs during the guidelines' formulation, the authors prompted the initiation of the multicenter collaborative prospective cohort study SINPHONI (Study of Idiopathic Normal Pressure Hydrocephalus on Neurological Improvement).[4] The resulting data supported the benefit of CSF shunt placement, regardless of tap test findings for cases with suspected iNPH based on clinical presentation, and who exhibit features of the so-called disproportionately enlarged subarachnoid-space hydrocephalus (DESH) on magnetic resonance imaging (MRI), that is, ventricular enlargement accompanied by shrinkage of the subarachnoid space at cerebral high convexities ("high-convexity tightness").[5] In light of these findings, in the second edition published in 2012, the guidelines' diagnostic flowchart was revised to give the deserved priority to MRI features of DESH.[6] Subsequently, Japan has seen a deluge of well-supported evidence produced by SINPHONI-2 (a randomized control trial (RCT)[7,8] and a national epidemiological survey,[9,10] among other studies. In this edition, the authors have revised the guidelines once again to reflect this new evidence, under the framework of a joint undertaking between the Japanese Society of Normal Pressure Hydrocephalus and the investigators involved in Etiology, Diagnosis, and Treatment of Idiopathic Normal Pressure Hydrocephalus, a research project for rare/intractable diseases, which is sponsored by the Ministry of Health, Labour and Welfare.

Objective of the guidelines

The guidelines for the diagnosis and treatment of iNPH were developed primarily for use by clinical specialists who often encounter neurological diseases

in the elderly (e.g., neurosurgeons, neurologists, and psychiatrists), and also to assist practicing clinicians in gerontology, internal medicine, radiology, rehabilitation, and primary care. The guidelines explicitly adopt the tenets and standards of evidence-based medicine; however, readers should not interpret this to mean that all recommendations and proscriptions in the document are based on well-supported evidence, noting that "expert opinions"—the lowest standard—are also cited as warranted. The ultimate goal of creating, disseminating, and implementing these guidelines is to provide the field with diagnostic criteria that can identify iNPH patients who would benefit from CSF shunt placement and achieve persistent long-term efficacy following treatment while preventing the condition from being overlooked in the elderly.

That being said, readers should bear in mind that these guidelines are not intended to supersede individual doctors' judgments in selecting diagnostic and therapeutic strategies. Moreover, other clinical policies may exist besides those explicitly detailed in these guidelines.

Method of Creating the Guidelines

Revision history, levels of evidence, and recommendation grading determinations

We drafted candidate clinical questions (CQs) for each of the important clinical issues identified, selected reflective keywords, and conducted literature review. Since the last edition of the guidelines was published in 2012, the scope of the review was refined to works published in or after that year in principle, identifying references published as late as June 2019. For each outcome of interest, the body of evidence available was graded using a rating sheet created by members of the systematic review team. In addition, select papers located by manual searching were incorporated into the review if deemed necessary by the Guidelines Management Committee (GMC).

The systematic review was primarily conducted using a qualitative methodology, in part because a purely quantitative review was infeasible due to insufficient number of datasets. However, a quantitative systematic review was set as the non-binding objective, to the extent deemed possible by all GMC members, in accordance with committee policy.

These guidelines consist of answers and commentary for each of the CQs, and the key answer statements are shown for easy reference at the beginning of each chapter. Evidence level was assessed based on the body of evidence available for each outcome and for each study design (RCT, observational study, etc.), rather than for each work in isolation. Evaluation criteria took into account bias risk, indirectness, inconsistency, imprecision, publication bias, and other confounding factors. Guideline writing team members were responsible for drafting CQs, answers, and commentaries in designated areas; these were then discussed and decided upon by the entire GMC. The overall structure of the guideline follows in general the established algorithm of diagnosis and management of iNPH. By the steps and stages of the algorithm, there are indicators that show portions of the text in which details on the subject can be found.

Table 1 Levels of evidence and recommendation grades

Recommendation grade	
1 (Strong)	Recommended
2 (Weak)	Suggested
Strength of Evidence	
A	Strong
B	Medium
C	Weak
D	Very weak

Levels of evidence and grades of recommendation are shown in Table 1. Diagnostic methods and treatments are ranked using a combination of evidence level and recommendation grade: for example, "1A" refers to a strong recommendation with strong evidence; "1B," a strong recommendation with moderate evidence; "2C," a weak recommendation with weak evidence; and "2D," a weak recommendation with very weak evidence. Evidence level is indicated for all possible interventions, even in relation to CQs for which a recommendation grade is not given.

The resulting rough draft of guidelines was reviewed by GMC members in evaluation and coordination roles. Review was also requested of an external committee. In November 2019, we sought public comment, considered the input received, and revised the draft accordingly.

Idiopathic Normal Pressure Hydrocephalus as a Concept

iNPH originates from impaired CSF absorption in the absence of prior illness or injury that can cause it (such as subarachnoid hemorrhage, meningitis, etc.). Gait disturbance is the most prominent symptom of iNPH, but cognitive impairment and urinary incontinence are also common. The condition progresses gradually and is frequently seen in the elderly. Symptomatic improvement can be achieved by the surgical placement of a suitable CSF shunt device.

Note that one conventional definition of iNPH includes this provision: "symptomatic improvement

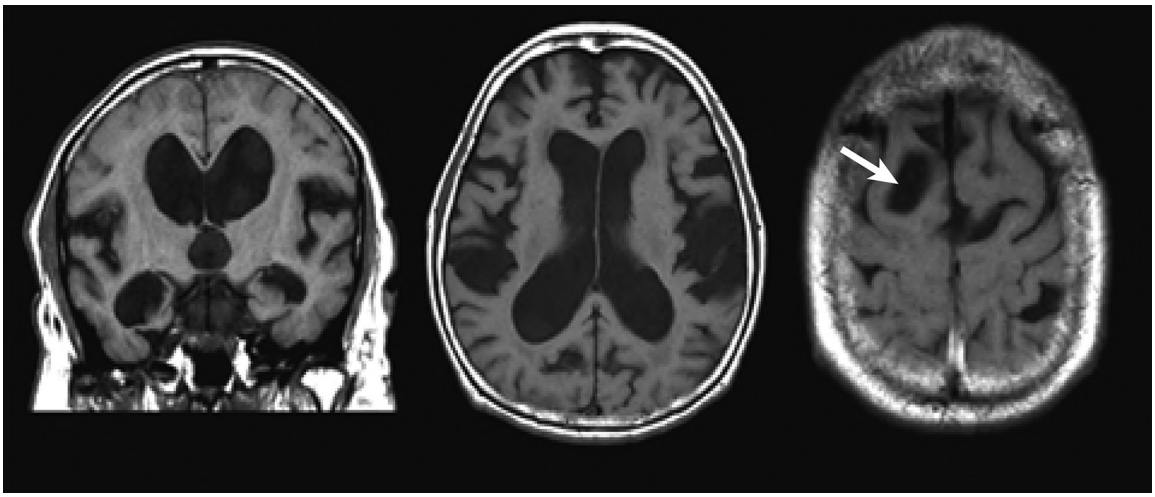

Fig. 1 DESH. Typical MRI of a patient with iNPH. Narrowing of the CSF spaces near the vertex and widening of the Sylvian fissure are good indicators that iNPH will respond to treatment. The few wide sulci that are seen on the cerebral convexity (white arrow) are all in the vicinity of large, superficial arteries. DESH: disproportionately enlarged subarachnoidspace hydrocephalus, MRI: magnetic resonance imaging, CSF: cerebrospinal fluid, iNPH: idiopathic normal pressure hydrocephalus.

achieved by CSF shunt placement." However, since this outcome can only be measured postoperatively, the definition is unsuitable for the preoperative diagnosis of iNPH. Hence, these guidelines refer to the description above as a "concept" rather than a definition of diagnosis *per se*.

The implications of using a "concept" lead to the introduction of stage-like progress in the establishment of the final diagnosis after performing shunt intervention with positive outcome. Before establishing the final diagnosis, several stages are required that will allow the selection of potential candidates for shunt treatment based on best available evidence, and these stages have been designated as suspected, possible, and probable (before shunt intervention) iNPH.

Hydrocephalus may be classified in a myriad of ways, including by time of onset, age, and even cause. However, the most important distinction depends on CSF circulation in the ventricular system, with normal and impaired flow along the CSF pathways, respectively, corresponding to the so-called communicating and non-communicating hydrocephalus. How a given case of hydrocephalus should be treated strongly depends on which of the subtypes it is. Traditional classification schemes give outsized attention to morphological changes in the ventricles and rarely consider eventual alterations in the subarachnoid space.

Disproportionately enlarged subarachnoid-space hydrocephalus

In the case of iNPH, the DESH plays an essential role in imaging diagnosis and decision for further management.[4,5] The history of DESH began with MRI volumetry-based investigation of the imaging features of iNPH patients by Kitagaki and colleagues.[5] The authors noted signs of high-convexity/midline subarachnoid space tightness in addition to mild–moderate ventricular enlargement on coronal MRI (Fig. 1). This morphological characteristic of CSF distribution was also observed in the vast majority of iNPH cases followed up in the SINPHONI study and needed further evaluation for its clinical significance. The SINPHONI-2 study clearly indicated that such patients, in combination with the clinical triad of symptoms, have high probability of positive tap test and benefit from shunting. As the degree of impairment of CSF absorption in the spinal cord subarachnoid spaces remains unresolved, DESH seems to be a reliable radiological marker of dysfunctional CSF absorption in the cranial subarachnoid spaces. In addition, this distinguishing aspect of hydrocephalus that was poorly engaged in traditional classification schemes will surely occupy an important place in future research of the disease.

How iNPH relates to similar types of hydrocephalus

The SINPHONI trial demonstrated the value of DESH findings on brain imaging—that is, ventriculomegaly (Evans index [EI] ≥0.3), in association with high-convexity/midline tightness and Sylvian fissure enlargement, which are both signs of impaired CSF dynamics in the subarachnoid space, in combination with the classic triad of symptoms in the diagnosis of iNPH.[4] Therefore, at the early diagnostic stages, imaging plays important role in differentiating

among the existing types of NPH. Ventriculomegaly (with EI ≥0.3) among iNPH patients enrolled in the SINPHONI study ranged from mild to moderate (average EI: 0.356 ± 0.040), with severe enlargement rarely encountered.[4] Debate is ongoing about how to handle patients with suspected iNPH who fail to meet this criterion (i.e., with an EI <0.3), or who do not exhibit high-convexity tightening. These presentations are difficult to distinguish from mere brain atrophy, and no systematic case series has been published till date. Therefore, we simply refer to such cases collectively as "non-DESH" in these guidelines, in anticipation of a formal definition of this subtype once more data become available.

sNPH develops after an obvious antecedent CNS disease or injury (subarachnoid hemorrhage and meningitis being representative examples). Diagnosing sNPH is unproblematic because there is usually history of a causal event/disease before the appearance of NPH symptoms and ventriculomegaly.

International iNPH guidelines published in 2005 define the age of clinical onset of NPH as ≥40 years, and that will inevitably include cases of delayed-onset congenital hydrocephalus.[11] In fact, one report claimed an unusually high prevalence of large head circumference (HC) among iNPH patients.[12] However, a major study of a large iNPH cohort found the average age of onset to be around 75 years, with very few individuals in their 40s at the time of onset.[13,14]

Other conditions under consideration as subtypes of delayed-onset congenital hydrocephalus include longstanding overt ventriculomegaly in adults (LOVA)[15] and panventriculomegaly with a wide foramen of Magendie and large cisterna magna (PaVM).[16] LOVA presents with severe lateral and third ventriculomegaly, as well as features suggestive of chronic intracranial hypertension (e.g., enlarged HC, and sella turcica enlargement and erosion). NPH-like symptoms (cognitive impairment, gait disturbance, and urinary dysfunction) start to appear in adulthood. Most cases of LOVA are non-communicating hydrocephalus accompanied by aqueductal stenosis. PaVM is characterized by enlargement of all cerebral ventricles and widening of the median aperture (of Magendie) and cisterna magna. The majority of cases exhibit pontine arachnoid septation and signs of restricted CSF dynamics in the pontine cistern. Moreover, the condition frequently co-occurs within families, suggesting a genetic component. Neuroendoscopic fenestration of the floor of the third ventricle could be indicated for LOVA and PaVM; however, some studies have reported successful symptomatic improvement in such patients following CSF shunt placement.[17,18] These two types of NPH are characterized by ventriculomegaly and NPH symptoms, and respond to CSF shunt placement in a similar way, a fact placing them in a single category of NPH that is separate from iNPH, without detectable etiology and regardless of the age of clinical onset. Given these distinctions, we would like to include these new categories within the NPH classification scheme: congenital/developmental NPH (Fig. 2). Some patients with NPH have familial aggregation, which is classified as familial NPH (Fig. 2).[19–21]

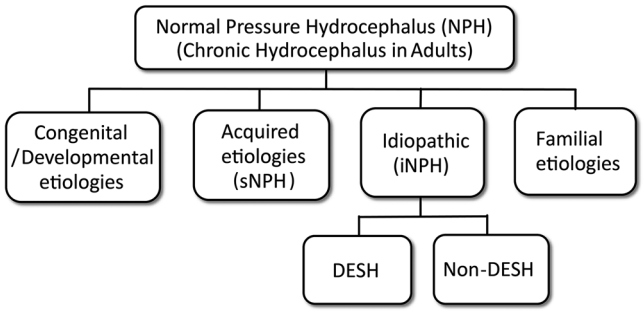

Fig. 2 Classification of hydrocephalus in Relation to iNPH. DESH: disproportionately enlarged subarachnoid-space hydrocephalus.

Epidemiology

The majority of epidemiological studies on iNPH have been hospital-based; however, there have been some reports of population-based studies on community residents. It is difficult to compare the results of previous studies since epidemiological studies on iNPH have involved different populations and survey methods. It is also important to note the clinical and statistical heterogeneity in the results presented within the studies, depending on their survey methods, populations, and surveyed years; for example, heterogeneity has been noted in the guideline used for the diagnosis of iNPH. Here, we present data from studies carried out in Japan and other countries after classifying epidemiological studies on iNPH into (A) population-based studies,[22–28] (B) hospital-based studies,[9,29–33] and (C) other epidemiological reports on iNPH.[34–36]

Population-based studies

The prevalence of iNPH according to the international guidelines in the general population, as reported by two recent Swedish retrospective epidemiological surveys[27,28] using head CT data, is 3.7%; prevalence rates of 8.9% and 5.9% were reported in the population aged 80 years and above in both studies, suggesting that prevalence increases with age. However, the prevalence of iNPH in one of the epidemiological surveys in Sweden would be 1.5%, if the researchers

had used the criteria of the Japanese guidelines.[27] This value is virtually consistent with a weighted average of 1.6% in four population-based studies in Japan.[22–24,26]

Hospital-based studies

In the hospital-based studies, the medical examination rate was reported to be 2–10 people per 100000,[9,29,30] but this value increased to 30–60 per 100000 among people aged 65–70 years and higher.[9,31] However, the indicators of incidence, such as medical examination rate and number of patients in hospital-based studies, are based on retrospective surveys that focused on imaging and examination records, which would fail to account for low medical examination rates and overlooked patients. Therefore, we need to be aware that more iNPH patients are present among the community-dwelling older population.

Other epidemiological reports on iNPH

Few prevalence surveys focusing on iNPH have been conducted on patients with diseases such as dementia, gait disturbance, and Parkinsonism. According to a 2018 meta-analysis of iNPH,[36] the mean prevalence of iNPH in the general population worldwide is 175 per 100000; it is 400 per 100000 in the population aged 80 years and above, indicating that the prevalence increases with age. The majority of epidemiological reports on this disease from Asia are from Japan, and the mean prevalence reported in these studies is 660 per 100000. However, the mean prevalence in countries other than Japan is 53 per 100000. The prevalence of iNPH in Asia, particularly in Japan, is higher than that in Europe or North America.

Asymptomatic ventriculomegaly with features of iNPH on MRI

Asymptomatic ventriculomegaly with features of iNPH on MRI (AVIM) was defined as asymptomatic cases that exhibit iNPH features on brain MRI.[24] Eight patients with AVIM were followed up for 4–8 years in a Japanese community-based study: in that time, four of them developed iNPH (corresponding to an incidence of 6–12% per year). Thereafter, 27 of 52 AVIM cases followed up in a Japanese hospital-based multicenter study developed iNPH within 3 years (incidence of 17% per year). This makes it clear that asymptomatic patients who exhibit features of iNPH on brain MRI should be monitored carefully due to the high risk of progressing on to iNPH.

Algorithm of Diagnosis and Management

In five chapters, the process of diagnosing iNPH is illustrated as an algorithm and explained by answering 15 CQs (Fig. 3).

Diagnostic criteria for possible iNPH

Possible iNPH is diagnosed if the following criteria are met:

1. More than one symptom in the clinical triad: gait disturbance, cognitive impairment, and urinary incontinence
2. Above-mentioned clinical symptoms cannot be completely explained by other neurological or non-neurological disease.
3. Preceding diseases possibly causing ventricular dilation (including subarachnoid hemorrhage, meningitis, head injury, congenital/developmental hydrocephalus, and aqueductal stenosis) are not obvious.

Diagnostic criteria for probable iNPH

Probable iNPH is diagnosed if a patient has all of the following three features.

1. Meets the requirements for possible iNPH
2. CSF pressure of 200 mmH_2O or less and normal CSF content
3. One of the following two investigational features:

(a) Neuroimaging features of narrowing of the sulci and subarachnoid space over the high-convexity/midline surface (DESH) with gait disturbance: small stride, shuffle, instability during walking, and increase in instability on turning

(b) Improvement of symptoms after CSF tap test and/or drainage test

Diagnostic criterion for definite iNPH

The diagnosis of definite iNPH is made when objective improvement of symptoms is shown after CSF shunt surgery. This category is synonymous with "shunt responder."

Chapter 1: Clinical Presentation and Initial Imaging Data

iNPH can be suspected on grounds of clinical and/or imaging data.

1. Characteristics and evaluation of gait disturbance

CQ-1. What methods are available for the evaluation of gait disturbances that are characteristic of iNPH?

The degree of severity of gait disturbance can be adequately evaluated by the currently used iNPH grading scale (iNPHGS). It is recommended as a subjective evaluation scale along with other objective and quantitative evaluation methods, such as the timed up & go test (TUG) and short-distance straight walking test.

Recommendation Grade 2, Level of Evidence C

Gait disturbance in iNPH has three characteristics: small-step gait, magnet gait, and broad-based gait.[37–42] Walking becomes unstable and slow.[41,43]

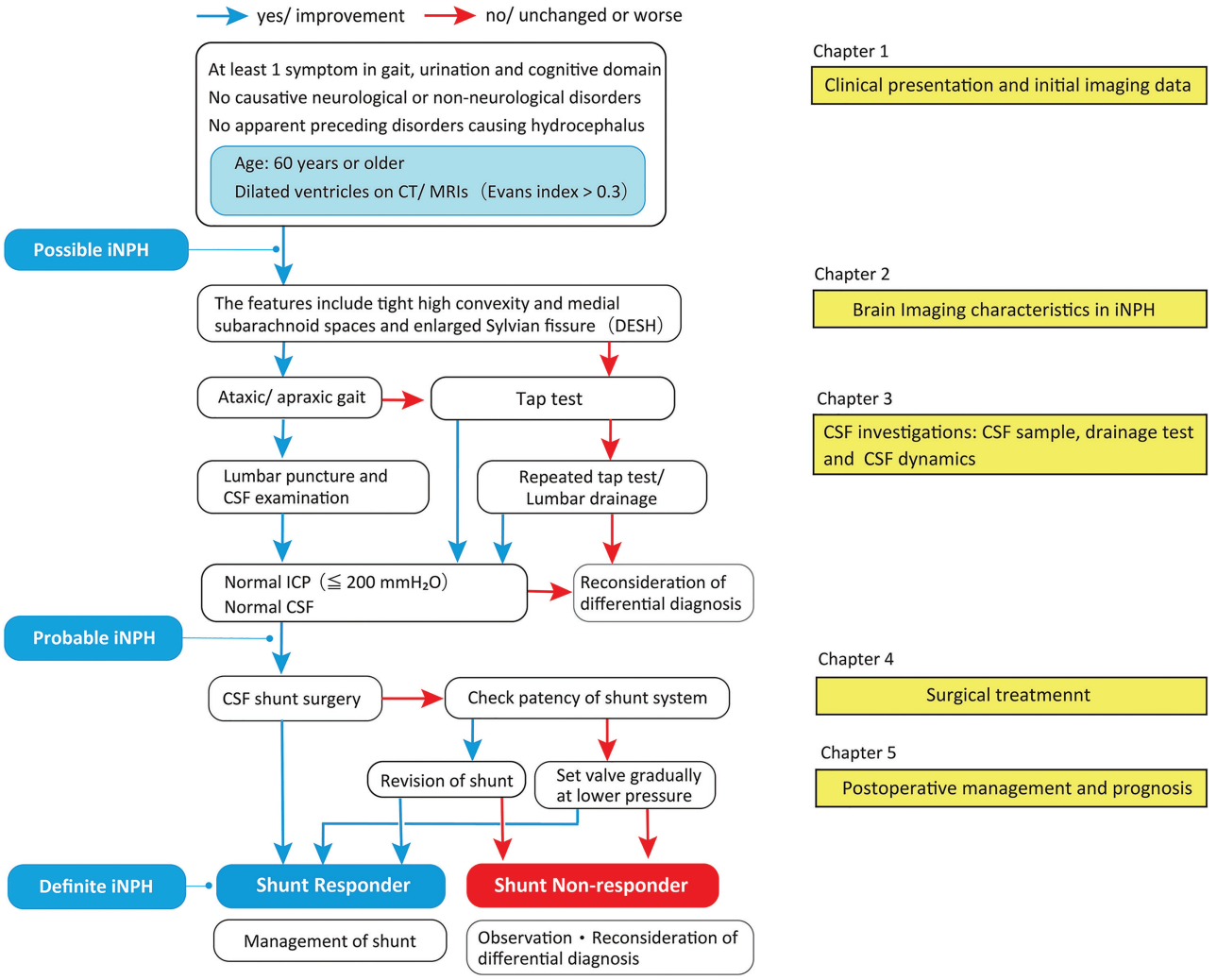

Fig. 3 Idiopathic normal pressure hydrocephalus: algorithm of diagnosis and management.

Table 2 iNPH grading scale

Grade	Gait disturbance	Dementia	Urinary incontinence
0	Normal	Within normal range	Absent
1	Unstable, but independent gait	No apparent dementia but apathetic	Absent but with pollakiuria or urinary urgency
2	Walking with a cane	Socially dependent but independent at home	Sometimes at night
3	Walking with two canes or a walking frame	Partially dependent at home	Sometimes during the day
4	Walking not possible	Totally dependent	Frequent

iNPH: idiopathic normal pressure hydrocephalus.

When changing directions, steps are small and unstable.[37,44] Moreover, patients walk duck-footed, and the length of the strides markedly fluctuates while walking.[40,41] Freezing gait may become marked when patients first start to walk, when they are walking in a narrow place, or when they change direction.[39] Unlike in Parkinson's disease, external triggers such as command lines and landmarks have little effect on improving gait.[41] Before CSF drainage is performed, the effect of practicing cannot be seen

when performing a multiple-step test.[45] The degree of severity of gait disturbance is described by the currently used iNPHGS (Table 2).[46] It is recommended to be used as a subjective evaluation scale along with other objective and quantitative evaluation methods such as TUG test and short-distance straight walking test.[47] Falls are known to occur readily in iNPH patients due to balance disorders, postural reflex disorder, instability, and difficulty in getting up from a chair. Patients should be interviewed to obtain a history of their falls. Although the mechanism of gait disorders is unknown, an association with the striatum[48] and the corticospinal tract has been previously reported.[49]

iNPH grading scale

In 2004, the Japanese committee for the first edition of this guideline proposed iNPHGS.[3] Thereafter, the reliability and validity of the iNPHGS were verified.[46] The scale items are set according to the worsening of the respective symptoms, and the levels are set to be easily defined and distinguished (e.g., for urinary incontinence, the frequency of incontinence events can be distinguished by a specific number). This was done with the purpose of adapting the scale to patients with a wide range of symptom severity. Moreover, another feature is that the item "subjective only" has been set for gait disturbance and cognitive impairment. This is because, in the early stages of iNPH, patients may be unsteady and forgetful but have no definite, objective abnormal findings. In iNPHGS, gait disturbance, cognitive impairment, and urinary incontinence are each evaluated on a scale from 0 to 4. The total score can be used as an index, together with the evaluation points for each of the three conditions.

2. Characteristics and evaluation of cognitive impairment

CQ-2. What methods are available for the evaluation of cognitive impairment in iNPH?

The Mini-Mental State Examination, the Wechsler Adult Intelligence Scale-III digit symbol coding and symbol search tasks, and the Frontal Assessment Battery are the recommended cognitive function tests. The Rivermead Behavioral Memory Test, a parallel test, is a recommended memory test.

Recommendation Grade 2, Level of Evidence C

Even in cases of iNPH with mild symptoms, psychomotor speed is declined, and attention and working memory are impaired.[39,50–57] Although memory impairment is also observed in mildly affected patients, memory recognition is often preserved in them compared to their impairment of free recall. In addition, poor performance in word fluency tests can be seen. These functions, which are susceptible to iNPH, are closely related to the frontal lobe. Patients with severe iNPH present with generalized cognitive impairment.[50] Patients with extensive cognitive impairment have a long duration of illness and severe motor impairment. Compared with patients with Alzheimer's disease, those with iNPH have milder disorientation and memory impairment, and greater frontal lobe dysfunctions such as attention impairment, declined psychomotor speed, impaired verbal fluency, and dysexecutive syndrome.[39,53] There is no learning effect even if cognitive function tests are repeated several times before CSF drainage.[45] Cognitive impairment progresses in iNPH, unless the patient receives CSF shunting.

Although the pathophysiology of cognitive impairment in iNPH is unknown, it may have a common pathophysiology of onset as the gait disturbance.[39,48,49] Areas that have been linked to cognitive impairment include the corpus callosum,[57] the medial frontal lobe (including the superior frontal gyrus), the anterior cingulate gyrus,[58] and the striatum.[48]

Cognitive impairment in patients with iNPH is evaluated with observational scales that focused on attention and memory impairment in daily living[37,59,60]. Cognitive impairment is also evaluated with cognitive tests including memory tests,[51,61–63] psychomotor speed tests,[51,61,63] attention tests,[51,61,62,63] verbal fluency tasks,[62] visuospatial tests,[62] and comprehensive cognitive tests.[63]

The representative cognitive tests are the Mini-Mental State Examination[64] (MMSE, which can evaluate a wide range of cognitive functions), the Wechsler Adult Intelligence Scale-III (WAIS-III) digit symbol coding and symbol search tasks, which can evaluate psychomotor speed, and the Frontal Assessment Battery (FAB), which can evaluate frontal lobe function, are the recommended cognitive function tests for patients with iNPH.[65]

In iNPH patients, in whom cognitive function is readily impaired and can be improved with CSF drainage, the tests generally focus on psychomotor speed, attention function, working memory, and memory function. However, psychomotor speed, attention function, and working memory also support other cognitive functions to work smoothly; therefore, improving these functions may likely improve the results of various other cognitive function tests. The international and Japanese (2nd Edition) guidelines on iNPH recommend MMSE because it is used worldwide and has been used till date in many iNPH studies. However, since memory function is relatively preserved in iNPH patients, it is desirable

to change the word stimulus in the three-word memory tests when the MMSE is performed repeatedly over a short period.

Tests that can evaluate psychomotor speed and can be used in Japan include the digit symbol coding and symbol search tasks included in WAIS-III.[66] The fact that these tests have been standardized and much data have been published on them makes them easy to use. The Trail Making Test (TMT), especially task A, seems to reflect psychomotor speed intuitively and has been used in previous iNPH studies due to its simplicity.[50]

The Stroop Test, which evaluates selective attention and suppression, and the Grooved Pegboard Test, which evaluates manual dexterity, have also been reported as useful tests for evaluating improvement after shunt intervention.[66] The Rivermead Behavioral Memory Test (RBMT),[67] which has been standardized and has four parallel tests,[68] is a useful memory test. To shorten the test time, some subtests in the RBMT, such as story recall and picture recognition, can also be used. The Ray Auditory Verbal Learning Test (RAVLT) that evaluates verbal memory has also been reported as useful in diagnosing iNPH.[69]

3. Behavioral and psychological symptoms of dementia (BPSD)

Similar to other dementia disorders, iNPH also presents with behavioral and psychological symptoms of dementia (BPSD) frequently. In iNPH, abulia/apathy, depression, and anxiety have been commonly reported.[70] A BPSD survey conducted in Japan reported that apathy was seen at a rate of 70.3%, which was a very high incidence, followed by anxiety (25.0%).[71] Compared with Alzheimer's disease, the frequency and severity of delusions, excitement, irritability, and depression were lower. The frequency of wandering and other abnormal behaviors was low, and stands at around 10%.[72]

Apathy in iNPH has been reported as being associated with dysfunction of the caudate nucleus,[73] gait disturbance, dementia, and urinary incontinence.[72,74,75] Similar to the triad, it should be considered an important symptom of iNPH, particularly due to its high incidence and effect on the burden of caregiving.

4. Characteristics and evaluation of urinary incontinence

No sufficiently strong evidence to make recommendations regarding characteristics and evaluation of urinary incontinence has been found. Urge incontinence associated with an overactive bladder is characteristic of dysuria in patients with iNPH. Among patients with iNPH, 90.9% experience urine dribbling, and 74.5% urinary incontinence.[76] In an urodynamic test, detrusor hyperactivity was seen in about 70% of patients, and bladder volume was approximately 200 mL, which is significantly smaller than the adult average. Moreover, decrease in maximum urine flow rate and increase in residual urine volume have also been observed.[76–78] Functional urinary incontinence and urge incontinence are said to be common in dementia.[79,80] Functional incontinence is suggested to affect urge incontinence due to an overactive bladder in iNPH.[72]

5. Frequency of onset of the triad and its components

Studies that have reported in detail the frequency of onset of various symptoms of iNPH have been mainly hospital-based. The percentage of gait disturbance is 94–100%, which is consistent in almost all studies and is seen in almost all iNPH cases.[4,9,54,60,81,82] The rates reported for cognitive impairment and urinary dysfunction vary, being 78–98% and 60–92%, respectively. Consistently, gait disturbance is the most common symptom of iNPH, followed by cognitive impairment and urinary incontinence. Many reports state that the triad is complete in approximately 60% of cases.[7,54,81] Meanwhile, a large-scale questionnaire survey conducted in Japan in 2012 revealed that the full triad was present in only 12.1% of 1524 patients.[9]

6. Symptoms other than the triad

In a study that evaluated neurological symptoms in 26 patients with iNPH, 84% had a snout reflex, 77% had an eyebrow reflex, 65% had paratonia (Gegenhalten), and 61% had a palmar reflex (palmomental).[83] Moreover, a report stated that 55% of iNPH patients had bradykinesia.[84]

In a study that compared eight patients with iNPH, eight with Parkinson's disease, and eight healthy controls, the iNPH group had decreased speed when lifting things and used more strength to grip things as compared to the healthy control group. This resembles the involuntary motor dysfunction of the upper limbs seen in Parkinson's disease.[85,86] However, among 127 patients with definite iNPH, Lewy body disease (LBD) was suspected in 21, and metaiodobenzylguanidine myocardial scintigraphy revealed decreased accumulation in 7 patients.[87] These observations were probably due to the coexistence of Parkinson-related diseases.

Chapter 2. Brain Imaging Characteristics in iNPH

Initial imaging evaluation

iNPH is suspected when an imaging investigation detects ventricular enlargement as a preliminary diagnostic information. This finding serves as an indication for further clinical and imaging evaluation and referral.

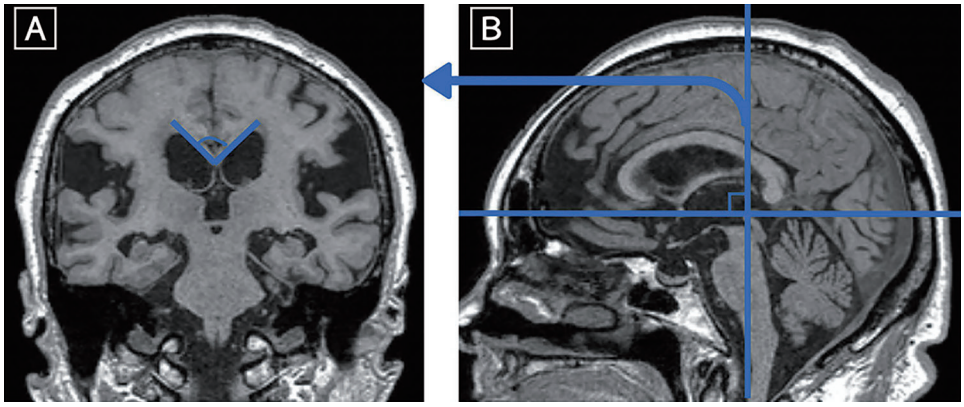

Fig. 4 Callosal angle. (A) The callosal angle, which is the angle between the left and right parts of the corpus callosum (superior walls of ventricles) should be measured on the coronal plane, (B) on a slice through the posterior commissure and perpendicular to the anterior commissure–posterior commissure line.

The most important finding in hydrocephalus is ventriculomegaly. The ratio of the maximum width of the frontal horns of both ventricles to the intracranial space width (to the inner tables of skull bone) at that site—the EI—is used to evaluate ventriculomegaly. Hydrocephalus is defined as EI >0.3. As ventriculomegaly can also occur as an age-related change and in neurodegenerative diseases, it cannot be used as a sign for excluding neurodegenerative diseases; moreover, ventriculomegaly can be seen in healthy elderly individuals. In patients who do not have EI >0.3, but have clinical criteria leading to the suspicion of iNPH, further detailed imaging, preferably with MRI, should be carried out for detection of other imaging iNPH signs.

Shape and size of the cerebral ventricles and cerebral sulci

CQ-3. What images are useful for evaluating the characteristic findings of iNPH?

DESH findings—ventriculomegaly, Sylvian fissure dilation, and narrowing of the high convexity/midline subarachnoid spaces—are specific as iNPH imaging findings, with high positive, but low negative predictive values. Steepening of the callosal angle (CA) is available as an indirect index of the DESH findings and is useful in diagnosing iNPH and predicting the effect of a shunt intervention.

Recommendation Grade 2, Level of Evidence, C

Morphological evaluation by CT or MRI is essential not only for screening but also for diagnosing iNPH. MRI is excellent for evaluating morphological changes, and coronal plane images are particularly useful for evaluating DESH—ventriculomegaly, Sylvian fissure dilation, and narrowing of the high parietal convexity/midline subarachnoid spaces.[4] If imaging in the axial plane is performed up to the most superior (fronto-parietal) cortical areas, the diagnostic performance could be equivalent to that of coronal plane imaging.[88]

Enlargement of the cerebral ventricles is considered a cardinal observation in iNPH patients,[5,88–91] and the historically used EI >0.3 is defined as the maximum width of both frontal horns of the lateral ventricles divided by the maximum intracranial width on the same slice. Although a lot of patients with iNPH have EI >0.3, in some cases its value is 0.3 or less. The subarachnoid spaces are wide at or below the Sylvian fissure and narrow in the high parietal convexity region.[5,88,92–94] Additionally, some cerebral sulci may be isolated and enlarged in an oval shape (Fig. 1).[5] In other words, CSF is retained in the subarachnoid spaces located below the level of the lateral cerebral ventricles and Sylvian fissure, whereas the high parietal convexity/midline subarachnoid spaces are reduced, that is, CSF in the subarachnoid spaces exhibits an uneven distribution. Currently, it is being proposed that hydrocephalus with such characteristics should be called DESH.[4] DESH is highly sensitive and specific and can be distinguished from atrophy in Alzheimer's disease.[5,92,93] Further on in iNPH management, if a patient has at least one of the triad symptoms and DESH findings on MRI, a positive response to the tap test can be expected,[94] and the effectiveness of the shunt intervention will be high.[4] DESH findings normalize after shunt intervention.[22,51] Some elderly individuals have findings similar to DESH on MRI, even though they are asymptomatic (AVIM). Some of them were reported to become symptomatic a few years later.[24]

Among patients diagnosed with iNPH, DESH findings were reported in 64% and non-DESH

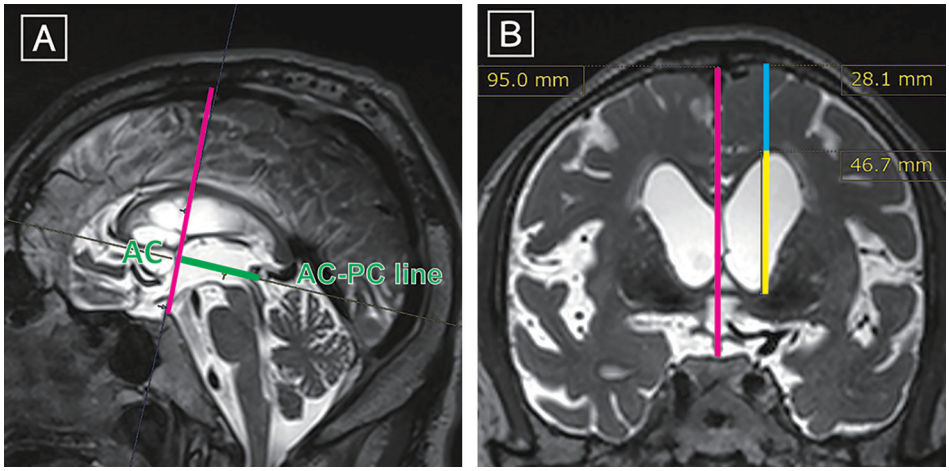

Fig. 5 z-EI and BVR. Evaluation of the z-EI and BVRs should be done on the coronal plane, (A) on a slice through the anterior commissure and perpendicular to the AC-PC line (green). (B) The height of the frontal horns of the lateral ventricles (yellow line) in the z-axis divided by the midline diameter of the skull (magenta line) is defined as the z-EI, with a cutoff value of 0.42. The BVR at the AC levels are measured as the maximum z-axial length of the brain just above the lateral ventricles (yellow line) divided by the maximum length of the lateral ventricles (cyan line). When the coronary plane is through the AC, the value will be below 1.0, and when the plane is through the PC, it is below 1.5. This figure shows z-EI = 46.7/95.0 = 0.49 >0.42, BVR at the AC level = 28.1/46.7 = 0.6 <1.0. AC-PC: anterior commissure–posterior commissure, BVR: brain/ventricle ratio, z-EI: z-Evans index.

findings in 36%. However, with definite iNPH diagnosis, a 77% positive predictive value was shown, while the negative predictive value was as low as 25%.[95] This shows that iNPH should not necessarily be judged only based on DESH findings. In addition to DESH, there are some other specific imaging characteristics that have been observed. Callosal angle (CA), which is defined as the angle between the left and right parts of the corpus callosum (superior walls of the ventricles) and measured at the slice through the posterior commissure (PC) and perpendicular to the anterior commissure–posterior commissure (AC–PC) line, is the index that indirectly expresses DESH (Fig. 4). CA <90° is seen in most iNPH cases.[96] Since CA greatly differs depending on the measurement position and measurement method, it is necessary to standardize the measurement method. The diagnostic value of CA has been also confirmed by reports that it helps to predict the effect of shunt intervention.[97,98] Its ability to differentiate iNPH from Alzheimer's disease has a sensitivity of 97%, a specificity of 88%, and a positive predictive value of 93% at a cutoff value of 90°.[96] Enlargement of the lateral ventricles in iNPH usually occurs vertically on the coronal plane (z-axis) rather than along the axial plane (x-axis).[99] Therefore, the z-EI, which is defined as the height of the frontal horns of the lateral ventricles in the z-axis direction divided by the midline diameter of the skull, with a cutoff value of 0.42 is superior to EI >0.3 (Fig. 5A).[99] In the same coronal plane, the brain per ventricle ratios (BVRs) at the AC and PC were calculated as the maximum width of the brain just above the lateral ventricles divided by the maximum width of the lateral ventricles on the reference coronal planes at the AC and PC levels, respectively.[100] BVR measured at the slice through the AC and perpendicular to the AC–PC line is <1.0 in iNPH (Fig. 5B), and BVR measured at the slice through the PC is <1.5. In addition, expansion of the inferior horn of the lateral ventricle has been reported to be useful for predicting the effectiveness of a CSF shunt intervention.[96] Therefore, even if EI is <0.3, but the other indices meet the conditions of expanded inferior horn of the lateral ventricle, such as CA <90°,[96,101] z-EI >0.42,[99] BVR at AC level <1.0, and/or BVR at PC level <1.5,[100] it is acceptable to diagnose possible iNPH. Moreover, a sagittal plane MRI will reveal that the posterior part of the cingulate sulcus is narrower than the anterior (in healthy controls, either they are equal, or the anterior part is narrower than the posterior).[102] All these findings are useful for differential diagnosis from Alzheimer's disease.

Compared to Alzheimer's disease, atrophy of the hippocampus is mild in iNPH[103] and dilation of the parahippocampal sulcus is not so significant.[5,89,91] It has been reported that the cross-sectional area or diameter of the midbrain decreases in iNPH and correlates with gait disturbance,[104] and that the midbrain diameter increases after a shunt intervention.[105] However, there are conflicting reports[106,107]

stating the opposite, and the diagnostic value of these findings is not yet clear. Similar observations have been reported that the cross-sectional area of the corpus callosum in iNPH is smaller than in healthy controls and that it increases after shunt intervention, the degree of increase correlating with improvement in cognitive impairment.[57] In brief, cerebral ventricles, Sylvian fissure, high convex cortical, and medial CSF volumes, intracranial volume ratio, and subarachnoid spaces vertical volume ratio are reported to be useful for differentiating iNPH from Alzheimer's disease.[99,101,108–110] Again, the diagnostic value (power of evidence) of these last observations remains unclear.

Changes in the deep periventricular white matter

CQ-4. Is it recommended to utilize advanced diffusion MRI in addition to standard MRI scans for patients with suspected iNPH?

Abnormalities are found in the diffusion index of nerve fibers by diffusion tensor imaging, mainly in the periventricular and deep white matter, and increased fractional anisotropy of the dispersion in the corticospinal tract is characteristic.

Recommendation Grade 2, Level of Evidence C

Changes in the deep periventricular white matter (the so-called leukoaraiosis) on CT and MRI are more frequently observed in patients with severe iNPH, compared with healthy elderly individuals. It is not an essential finding, but rather suggests associated ischemic complications.[61,111] The extent of change in the white matter has been reported to be inversely correlated with the tap test response.[43] However, improvement of changes in the deep periventricular white matter after shunt intervention has yielded controversial results.[59,112]

Diffusion tensor imaging (DTI) is also reported to be useful for diagnosis of iNPH.[113–115] Abnormalities in the periventricular white matter on DTI are detected in iNPH patients, and the finding of increased fractional anisotropy (FA) in the corticospinal tract is specific to iNPH.[116–124] Changes in the quantitative value after a shunt intervention have been reported to be correlated with the level of improvement in the clinical symptoms.[114,122]

Furthermore, studies using diffusion kurtosis imaging,[125] q-space imaging,[126] and neurite orientation dispersion and density imaging[127,128] as advanced diffusion MRI techniques have been conducted. However, for these last methods, there are only a few reports, and their diagnostic value has not been established.

Other imaging methods

The studies on phase-contrast MRI reported that CSF flow velocity, pulsatile flow, stroke volume, and pressure gradient in the cerebral aqueduct significantly increase in iNPH.[129–131] The sensitivity and specificity of aqueductal stroke volume for diagnosis of iNPH were reported as 78–85% and 100%, respectively.[130] It has also been reported that the stroke volume and reversed flow rate can predict the effect of shunt intervention[132–134] and tend to normalize after the intervention.[134] Their measurement accuracy has been verified in recent years.[135] However, the superiority of high aqueductal stroke volume on phase-contrast MRI over other imaging indices is not clear, and its diagnostic value has not been established.

It has been reported that proton magnetic resonance spectroscopy shows significant decrease in the N-acetylaspartate/creatine (NAA/Cr) ratio in the frontal lobe white matter and thalamus[136,137] and a peak in lactate is seen in the cerebral ventricles in iNPH.[138] Although the NAA/Cr ratio reportedly increases after surgery and correlates with improvement in cognitive function,[58] there are also negative reports,[139,140] and its diagnostic value has not been established.

Nuclear diagnostic methods

CQ-5. What are the characteristic nuclear medicine findings of iNPH?

Nuclear medicine diagnostic methods such as single-photon emission computed tomography show decreased cerebral blood flow in the anterior parts of the cerebral hemisphere and Sylvian fissure periphery, and increased blood flow in high cortical areas (convexity apparent hyperperfusion [CAPPAH] sign).

Recommendation Grade 2, Level of Evidence B

Cerebral blood flow (CBF) pattern on single-photon emission computed tomography (SPECT) reflects the morphological changes of DESH in iNPH. The finding on SPECT is decreased CBF around the Sylvian fissure and relatively increased CBF around the high parietal lesion. This CBF pattern, which is specific to iNPH, is called convexity apparent hyperperfusion (CAPPAH).[141,142] The CBF pattern of hypoperfusion around high parietal lesion was confirmed in 58% of patients with the frontal dominant hypoperfusion type, 12% with the posterior dominant type, and 30% with the mixed type, but the effect of shunt intervention could not be predicted.[143] CBF around high parietal lesion in the shunt-effective group was reported to be lower than

in the shunt-non-effective group. Acetazolamide-enhanced SPECT showed that increase in CBF after acetazolamide administration could predict improvement in cognitive function of iNPH patients after shunt intervention.[144] However, the acetazolamide test on SPECT is not commonly performed in suspected iNPH patients. In the iNPH patients who had improved urinary incontinence after shunt intervention, CBF in the middle cingulate gyrus was increased after the shunt intervention.[145] Urinary incontinence was also reported to be correlated with decreased CBF in the right frontal lobe.[146]

Some more recent nuclear diagnostic techniques, such as dopamine transporter scintigraphy, have been studied in iNPH.[147] However, there are still no well-constructed reports on dopamine transporter scintigraphy in iNPH, and evidence of its usefulness is awaited.

A study on fluorodeoxyglucose-positron emission tomography (FDG-PET) reported that decreased glucose metabolism in the basal ganglia is useful for differentiating iNPH from other degenerative diseases.[148] In addition, decreased cerebral glucose metabolism in iNPH improved after shunt intervention.[149,150]

Amyloid positron emission tomography (PET) study reported that amyloid deposition was observed in some cases of iNPH.[151–154] However, amyloid deposition does not necessarily signify Alzheimer's pathology and its presence will not exclude the need for shunt intervention.

Chapter 3. CSF Investigations: CSF Sample, Drainage Test, and CSF Dynamics Investigation

The CSF drainage test (tap test)

CQ-6. Do the tap test and continuous drainage test have predictable therapeutic efficacy?

The CSF drainage test (tap test) is useful for diagnosing iNPH and predicting the therapeutic effect of a shunt intervention.

Recommendation Grade 1, Level of Evidence B

CQ-7. How soon after a CSF drainage test should the results be evaluated?

It is recommended that the CSF tap test is evaluated within 24 hours after CSF removal and multiple evaluations should be done for up to a week. Cognitive impairment and urinary dysfunction are expected to improve subsequently after gait improvement, but there is no established evidence regarding the timing of this.

Recommendation Grade 2, Level of Evidence C

The CSF tap test is widely used for diagnosing and predicting the therapeutic effect of a shunt intervention, based on the changes in clinical symptoms of gait disturbance, cognitive impairment, and urinary incontinence.[42,44,54,63,155–181] Although the changes in clinical symptoms before and after the CSF drainage test are evaluated using various scales around the world, the iNPHGS is widely used as a simple scale whose reliability and validity have been verified.[7,8,46,168,181–183] Objective and quantitative evaluations on TUG test, short-distance straight walking test, MMSE, and video-viewing rating of gait disturbance are recommended.[44,158,162,171,174,184,185,186] Congruently, pathological gait features, such as small-step gait (short length of stride), broad-based gait (increasingly large step intervals), instability, difficulty in changing directions, frozen gait (no first step taken), and shuffle (dragging of feet and decreased elevation), should be evaluated by video-viewing of the TUG test.

The CSF tap test has a sensitivity of 58% (26–87%) and a specificity of 75% (33–100%) as reported in systematic reviews.[169] If the triad symptoms improve after the CSF tap test, the diagnosis is highly likely to be iNPH, and the symptoms are expected to be improved by a shunt intervention. However, if a tap test does not result in any improvement, iNPH cannot be excluded, and caution is required regarding the possibility that the symptoms will improve (false negatives) by a shunt intervention.[161,162,165,169,170,174,177,178,181] In particular, the longer the period between appearance of symptoms and CSF drainage, the higher the frequency of false negatives. However, symptoms may improve after a shunt intervention, even if they do not respond to the tap test.[181]

There is controversy about whether to repeat the tap test, perform continuous drainage, or perform shunt intervention if a false-negative response to the CSF tap test is suspected. It has not been established whether the continuous CSF drainage test is more predictive of the efficacy of a shunt intervention than the CSF tap test. If both the typical symptoms (gait disturbance, cognitive impairment, and urinary incontinence) and imaging findings (DESH) are present, a shunt intervention is likely to improve the symptoms in the absence of other comorbidities.[7,8]

In the tap test, there is no difference in the positive detection rate, sensitivity, and specificity with respect to the amount of CSF removed, in the range of 30–50 ml.[23] The evaluation method and timing of assessing changes in clinical symptoms are more important than the volume of CSF removed. Evaluation should be performed 2–4 hours after the tap test and on the following day (approximately 24 hours later).[155,156,158,161,162,166,168,170,173,175,176,178,179,181] It should be performed at least on the following day, and as symptoms may improve from the following day

onward, it is recommended that evaluations be performed multiple times within the first week. In a single-center retrospective observational study, walking function improved on day 2 (48 hours later) after the tap test. However, the degree of improvement decreased after day 3.[173] In the SINPHONI-2 study, cognitive impairment and urinary incontinence tended to improve later than gait disturbance and were evaluated within one week of the tap test.[7,8] In addition, although there is a report stating that MMSE did not improve the day after the tap test but improved 1 week later,[167] evidence on the optimal evaluation time for changes in the respective symptoms has not yet been established.

Normal pressure (diagnosis)

CQ-8. Are "intracranial pressure monitoring" and CSF dynamics tests useful for diagnosing iNPH and determining indications for CSF shunt placement?

Intracranial pressure monitoring and CSF dynamics tests are useful for diagnosing iNPH and determining the indications for CSF shunt placement, particularly if basal CSF pressure is increased, frequency of B-waves during sleep is high, and CSF pressure pulse waves are high. High outflow resistance (Rout) of the CSF measured by infusion test correlates with effective shunt intervention.

Recommendation Grade 2, Level of Evidence C

(A) *Pressure and properties of CSF*

CSF is colorless and clear, like water. Although there are many reports stating that the upper normal pressure limit of CSF is 200 mmH_2O[54] or 180 mmH_2O,[1] even with values higher than this, the possibility of iNPH cannot be ruled out. It is necessary to exclude other diseases such as benign intracranial hypertension and carcinomatous meningitis. There is no clear documentation on the normal lower limit of CSF pressure in the elderly.

(B) *Continuous intracranial pressure measurement (ICP monitoring)*

The measurement time is approximately 12–48 hours, mainly at night. The measurement site is most commonly the lumbar cistern.[62,187–189] Pressures reportedly measured at other sites are cerebral parenchymal pressure,[187,190,191] intraventricular pressure,[62] and epidural pressure.[192,193] As such, the invasiveness of ICP measurement is high compared to the tap or infusion test. Therefore, it is only used when ICP monitoring becomes necessary, such as in cases where a lumbar puncture cannot be performed, and in those with marked enlargement of the cerebral ventricles if it is unclear whether they have arrested or symptomatic hydrocephalus.[187] This method is rarely used for diagnosing iNPH. The main parameters of ICP monitoring are as follows:

(1) Intracranial basal pressure

The threshold of basal pressure is set at around 7–15 mmHg, and most patients with iNPH have an upper limit of normal pressure. The value of the test is controversial: when basal pressure is high, the efficacy of a shunt intervention is assumed to be also high,[193–195] but there are cases in which there is no correlation.[190,191,196]

(2) Pressure wave

B-waves appear more frequently during sleep, especially during the rapid eye movement sleep phase.[189] The more frequently they appear (≥15% of all records), the more effective shunt intervention has been reported to be,[187,193] but there are also reports stating that there is no correlation.[62,189,191,197]

(3) CSF pulse pressure

In the effective shunt intervention groups of several studies, increase in amplitude and decrease in latency were observed,[62,195,197–199] and the average value (high wave relative frequency) of the three highest wave amplitudes was often 9 mmHg or higher (positive prediction rate of 96%). The correlation between amplitude and pressure is considered to be high.[62]

(C) *CSF infusion test*

The CSF infusion test is a method for examining CSF circulatory dynamics by injecting physiological saline or artificial CSF into the CSF spaces. The values differ according to the injection site (lumbar region),[51,166,187,193,200–202] infusion speed (constant speed of injection[51,187,193,202,203] or rapid infusion[201]), and ICP measurement site (lumbar subarachnoid space pressure[166,187,193,200,202] or epidural pressure[193]). There are many reports on the sustained CSF infusion method, mainly in Europe. However, the results are not affected by meningeal or brain parenchymal lesions. The rapid infusion and continuous infusion methods are widely used. The main parameters are as follows:

(1) CSF outflow resistance

As shunt intervention is a surgery that lowers the outflow resistance of CSF (Rout), measuring the Rout may be useful in predicting the effectiveness of a shunt intervention.[51,187,193,200] Rout has been found to be significantly higher in effective shunt intervention groups, and the positive prediction rate was reported to be ≥80%.[51,187,193,200] Many reports state that the absolute value of Rout and the effective/ineffective threshold is around 14–20 mmHg/mL/min (positive prediction rate 80–92%).[51,187,193,200] However, Rout measured in the spinal CSF compartment may not correctly reflect the Rout of the cerebral ventricular space or the entire cerebrospinal space. Moreover, there are cases in which a shunt

Table 3 CSF biomarkers for distinguish iNPH from normal control and Alzheimer's disease

	Differential diagnosis	Predict poor CSF shunt effect
Aβ42	No change compared to AD, lower than NC	Low value
p-tau	Lower than AD, no change compared to NC	High value
t-tau	Lower than AD, no change compared to NC	High value
NFL	Higher than NC	High value
LRG	Higher than NC	High value
Aβ38	No change compared to AD, lower than NC	
Aβ40	No change compared to AD, lower than NC	
PTPRQ	Higher than NC	
Brain-type transferrin	Lower than NC	

Aβ: amyloid β protein, AD: Alzheimer's disease, CSF: cerebrospinal fluid, iNPH: idiopathic normal pressure hydrocephalus, LRG: leucine-rich α2-glycoprotein, NC: normal control, NFL: neurofilament light chain, p-tau: phosphorylated tau, PTPRQ: protein tyrosine phosphatase receptor type Q, t-tau: total tau.

intervention was effective even though the Rout was low.[178,192,196,197]

The standard value of Rout differs according to the testing method used. It is not constant due to differences in injection conditions, and different standards have been set up. However, all reports agree that the efficacy rate of a shunt intervention is high when Rout is high.[178,187,192,193,195,200]

(2) CSF outflow conductance

CSF outflow conductance (Cout) is reported to be significantly lower in effective shunt intervention groups,[166,193,202] and the Cout effective/non-effective threshold is said to be 0.08 mL/min/mmHg (positive prediction rate of 74–76%).[166,200] However, there is no high-level evidence showing that it is useful for diagnosing iNPH.

CSF biomarkers

CQ-9. Which CSF evaluations are useful for diagnosing iNPH and predicting its prognosis?

Amyloid β42 (Aβ42) in the CSF of patients with iNPH showed lower values than in healthy subjects. Phosphorylated tau (p-tau) and total tau (t-tau) were low compared to patients with Alzheimer's disease. Measurement of Aβ42, p-tau, and t-tau in the CSF is useful for the differential diagnosis of Alzheimer's disease.

Recommendation Grade 2, Level of Evidence B

Although there is no CSF biomarker with high sensitivity and specificity that predicts the effect of a CSF shunt intervention, measurement of Aβ42, p-tau, t-tau, neurofilament light chain, and leucine-rich α2 glycoprotein in the CSF can be referenced for predicting the effect of a CSF shunt intervention.

Recommendation Grade 2, Level of Evidence C

CSF evaluation is important for differentiating secondary hydrocephalus due to conditions such as meningitis and subarachnoid hemorrhages. In recent years, CSF biomarkers have been measured to diagnose iNPH and distinguish it from other neurodegenerative diseases. Among these biomarkers, those that showed consistent results in at least two studies are presented in Table 3.

Aβ42, phosphorylated tau (p-tau), and total tau (t-tau) in CSF are the biomarkers with the most consistent results across studies. They can likely help to differentially diagnose iNPH and Alzheimer's disease/healthy subjects.[204–217] However, these have been reported as biomarkers that reflect pathological changes in Alzheimer's disease and are not specific markers of iNPH.

Leucine-rich α2 glycoprotein (LRG),[218] protein tyrosine phosphatase receptor type Q (PTPRQ),[219] and brain-type transferrin[220] were first identified in Japan as proteins that vary specifically in iNPH patients based on a comprehensive proteomic analysis of CSF protein. However, subsequent studies have shown that LRG is also increased in neurodegenerative diseases, such as progressive supranuclear palsy (PSP) and LBD, and have reported that it is not a specific marker for iNPH. It is reported that PTPRQ and brain-type transferrin are derived from the choroid plexus. PTPRQ increases and brain-type transferrin decreases in patients with iNPH as compared to healthy subjects and patients with Alzheimer's disease. However, the kinetics of these biomarkers in neurodegenerative diseases other than Alzheimer's disease is unknown, and it is necessary to verify their sensitivity and specificity for the diagnosis and differential diagnosis of iNPH in the future. There are still no biomarkers with strong evidence that can differentiate and determine the

coexistence of iNPH with neurodegenerative diseases, other than Alzheimer's disease and vascular dementia.

Although there are still no highly sensitive and specific CSF biomarkers that can predict the effect of a CSF shunt intervention, Aβ42, p-tau, t-tau, neurofilament light chain (NFL), and LRG have been reported in multiple studies.[221] However, these biomarkers do not specifically reflect the pathology of iNPH.

Chapter 4. Surgical Treatment

Effectiveness of shunt treatment

CQ-10. Which surgical methods most effectively ameliorate iNPH symptoms?

CSF shunt intervention is effective for treating iNPH.

Recommendation Grade 1, Level of Evidence B

Surgical methods applied for iNPH treatment, similar to the general surgical methods for communicating hydrocephalus, are shunt interventions with ventriculo-peritoneal (VP), ventriculo-atrial (VA), or lumbo-peritoneal (LP) shunts, and they are effective.

iNPH patients with severe white matter lesions were randomly allocated to a shunt patency group and a ligation group. Three months later, in the ligation group, patency was restored, and follow-up observation was performed up to 6 months post-surgery. Symptoms improved quickly in the shunt patency group. However, in the shunt ligation group, the symptoms did not improve during the 3-month ligation period after the surgery. Meanwhile, 3 months following this, after the ligation was removed, the symptoms were reported to improve.[222]

Around the world, VP shunt placement is commonly performed. However, in Japan, a nationwide survey in 2012 showed that VP shunts were made for 43.2%, LP shunts for 55.1%, and VA shunts for 1.7% of all treated iNPH patients.[9] Although the effects of each treatment method have been reported, no report has compared them in a prospective and randomized manner. The methods used to evaluate the effectiveness of shunt interventions differ according to the study, and there are differences in the improvement rates by symptom. In the SINPHONI-2 study, which is a multicenter randomized comparative study involving 20 institutions in Japan, it became evident that the LP shunt intervention was effective.[7] At least 1-point improvement on the modified Rankin Scale (mRS) and iNPHGS after 12 months of the shunt intervention were almost the same in patients treated with VP shunt surgery (SINPHONI) and those treated with LP shunt surgery (SINPHONI-2).[8] No significant difference between the surgical procedures was detected. The rates for serious adverse events were 22% in the LP and 15% in the VP shunt groups, respectively, and the corresponding values for non-serious adverse events were 27.6% and 20%. Complications due to CSF over-drainage are more common with LP than with VP shunts. After an LP shunt intervention, CSF may leak from the puncture site immediately after the puncture, and symptoms of over-drainage such as headache may appear. In this case, it may be preferable to place the patient on proactive bed rest rather than to change the valve pressure setting.

The Japanese nationwide survey also showed improvement on the mRS—in the VP shunt group (n = 417), it was from 2.73 (standard deviation (SD) = 0.76) to 2.01 (SD = 0.92), and in the LP shunt group (n = 540), from 2.66 (SD = 0.76) to 1.98 (SD = 0.93). The complication rates were 10% in the VP shunt group and 14% in the LP shunt group, without statistically significant difference between the two groups.[10] In cases of shunt malfunction due to obstruction, tube replacement was performed in about 1% of patients in the VP shunt group, but in 6.8% in the LP shunt group, which was clearly higher. Thus, LP shunts are not recommended if spondylosis is severe and CSF communication is hindered.

In addition, no statistically significant difference was found in the reports comparing surgical complications between the VA (n = 150, 36%) and VP shunts (n = 346, 42.5%). However, subdural hematomas due to CSF over-drainage were significantly more frequent in the VA shunt group (12.7%) than in the VP shunt group (5.5%) (p = 0.006). Shunt occlusion and repeated interventions were reported to be significantly less frequent in VA shunts (6.7% and 10.7%) than in VP shunts (15.3% and 28.9%).[223]

Cardiopulmonary complications, nephritis, and renal failure are recognized as serious complications of the VA shunt intervention.[224–228] However, the incidence of these is less than 1%. VA shunt is recommended in situations where intraperitoneal adhesions are expected, such as after multiple abdominal surgeries, but not recommended if heart disease is present.

The efficacy and safety of endoscopic third ventriculostomy (ETV) have been compared to those of VP shunts with fixed pressure valve in iNPH patients who responded to the tap test. An RCT of 42 Brazilian iNPH patients, in a systematic review of the Cochrane library, showed that 50% of patients who underwent ETV achieved symptomatic improvement 12 months after the surgical intervention, whereas the VP shunt intervention achieved improvement in 76.9% of the patients.[229] However, some patients with congenital/developmental and familial NPH such as PaVM[230] and LOVA,[15] which show

downward displacement of the floor of the 3rd cerebral ventricle may have also been included. A comparison of 652 patients who underwent ETV for iNPH and 12,845 patients who underwent VP shunt intervention from 2007 to 2010 in the USA showed a mortality of 3.2% vs. 0.5%, respectively, and surgical complication rates of 17.9% vs. 11.8%, respectively, suggesting that ETV has a higher risk compared to shunt intervention.[231]

iNPH as defined in these Japanese guidelines is clearly distinguished from late-onset congenital NPH, including PaVM, LOVA, and familial NPH. ETV treatment for communicating hydrocephalus with decreased CSF turnover is suggested to have no efficacy.

Shunt valve selection

CQ-11. Which type of CSF shunt should be utilized in treating iNPH?

A programmable-pressure valve is recommended. If intracranial hypotension is detected, a mechanism (anti-siphon/gravity device, etc.) to prevent excessive drainage should be added.

Recommendation Grade 1, Level of Evidence B

(1) *"Fixed" vs. "programmable" pressure valves*

The fixed pressure valve has the advantage of having a simple mechanism and lower cost. However, when the flow rate is too high or low, the valve needs to be replaced. In a comparison of the fixed-pressure and programmable-pressure valves used in communicating hydrocephalus, including iNPH, up to the 2000s, the shunt revision rate and incidence rates of subdural effusion and hematoma remained the same between the two types of valves.[232,233] A meta-analysis comparing fixed-pressure and programmable-pressure valves in 1702 hydrocephalus patients over the age of 16 years in seven studies showed no significant differences in catheter-related complications or infection rate. However, with the programmable-pressure valve, over- or under-drainage and shunt revision rates were significantly higher.[234] A meta-analysis of hydrocephalus patients, including 2,622 children, showed no significant differences between the fixed-pressure and programmable-pressure groups regarding shunt survival rate and overall complications at 1 year. However, the shunt revision rate and over- and under-drainage rates were significantly lower in the variable pressure group. The programmable-pressure valves were reported to be particularly useful for adult patients 18 years and older.[235] In a meta-analysis of 33 studies on iNPH patients published in 2018, the rate of symptomatic improvement was unchanged (76% vs. 74%) when the fixed-pressure and programmable-pressure types were compared. However, subdural fluid retention (9% vs. 12%) and reconstruction rates (12% vs. 32%) were reported to be significantly higher in the fixed pressure valve.[236] In terms of cost, a retrospective examination of 110 tap-positive iNPH patients revealed that many patients required shunt revision and surgery for a subdural hematoma in the fixed-pressure group. The cost of addressing the complications that arise with the use of the fixed-pressure valve was estimated to be offset using programmable-pressure valves.[237]

Selecting a programmable-pressure valve for iNPH patients is recommended because the pressure can be set flexibly according to the patient's activities of daily living and symptoms.

(2) *"With" vs. "without" over-drainage prevention mechanisms*

In recent years, additional mechanisms (anti-siphon/gravity device, etc.) have resulted in less subdural CSF collections and hematomas than are seen with a programmable-pressure valve that has been adjusted to low pressure, and management is more uniform. These findings have been observed in RCTs[238,239] and observational studies.[240–243] However, it is challenging for single valve groups to be compared, and in a comparison of the SINPHONI (VP shunt using single programmable-pressure valve) and SINPHONI-2 (LP shunt using programmable-pressure valve with siphon-guard system) studies in Japan, no differences were seen in the frequency of subdural effusion and hematoma.[8] Therefore, using an over-drainage prevention mechanism is not indispensable unless low pressure is set from the beginning. Even in a meta-analysis that compared shunt valves, no significant difference was observed in the symptom improvement rate, subdural fluid retention rate, and shunt revision rate between the single programmable-pressure valve with and without an over-drainage prevention mechanism.[236]

(3) *"Pressure" vs. "Flow" regulated valves*

As another valve mechanism, the flow-regulated control valve is hardly used because the flow rate may be affected by the position in which the valve is implanted and subcutaneous tissue pressure.[244] Comparisons between flow control valves and fixed pressure valves reported no differences in the rates of symptom improvement, infection, shunt malfunction, and subdural effusion.[245,246] Since programmable- pressure valves can be used, the significance of flow-regulated system is low at present.

Shunt complications

CQ-12. What strategies are available for minimizing the complications of shunt placement?

Some complications can be avoided by preparing and planning preoperatively, and paying attention to shunt malfunction after the shunt intervention, excessive drainage of CSF, and shunt infection.

Recommendation Grade 1, Level of Evidence C

Complications of shunt intervention include shunt dysfunction due to obstruction of the shunt tube, headache, shunt infection, and subdural hematoma, which is associated with over-drainage of CSF after the shunt intervention.[238]

Appropriate catheter placement

As the most important factor in shunt malfunction, it is necessary to pay special attention to proper cerebral ventricle puncture and catheter placement in VP and VA shunts.[247–250] For cerebral ventricular puncture, equivalent reliability has been reported for frontal horn (frontal approach) and occipital horn/trigonum punctures (parieto-occipital approach). In both cases, the procedure should not be performed by free-hand puncture, and the puncture point should be examined based on the preoperative imaging.[251] Imaging guides such as neuro-navigation and stereotaxy are useful for placing the cerebral ventricle catheters in proper position without interfering with structures such as the ventricular wall and choroid plexus.[247,248,252–254]

On the other hand, LP shunts have the advantage of not involving the risk of causing intracerebral hemorrhage because they are not directly invasive to the brain parenchyma like VP shunts. However, in the elderly who are potential iNPH patients, because spinal degenerative disease occurs frequently, diagnostic imaging of the entire spine should be done before surgery, and attention should be paid to shunt malfunction due to obstruction or rupture of the lumbar catheter. Placement of a lumbar catheter in the proper position by fluoroscopy-guided paramedian lumbar puncture increases safety and accuracy.[255–256] Besides, to prevent the tube from protruding out of the abdominal cavity, it is necessary to perform an insertion technique that eliminates all spaces through which the tube can potentially protrude or migrate under the skin.[8,257]

Preventing shunt infection

Infection of the shunt system is an important surgical complication that is directly related to further severe complications such as meningitis and peritoneal infection. A protocol should be devised that includes the following: patients should be put on antibiotics before the skin incision, double gloves should be worn during the procedure, the shunt device should be immersed in saline with antibiotics to minimize contamination from air, and antibiotics also should be injected locally into the surgical wound. These precautions have been reported as effective in preventing shunt infection not only in pediatric cases but also in adults aged 40–88 years (average 59 years).[258] Also, there have been reports stating that the use of antibiotic-impregnated catheters (AICs) has reduced shunt infection rate in pediatric patients.[259,260] Additionally, reports have asserted that shunt infection is significantly suppressed in NPH patients other than those with iNPH.[261] However, in patients for whom AICs are indicated, the risk of growth of resistant bacteria should be considered, and AICs should only be used as required.

Chapter 5. Postoperative Management and Prognosis

Initial valve pressure setting

CQ-13. How should the initial pressure settings of programmable-pressure valves be configured in iNPH patients?

Initial high pressure setting with gradual decrease until clinical response or over-drainage symptoms are observed can be the proper approach. An alternative can be setting initial pressure according to the body height and weight/gender table and implementing corrections if necessary.

Recommendation Grade 2, Level of Evidence C

The initial pressure setting method can be any of the following:

① Start from high pressure and gradually lower it while observing the symptoms to find the optimal pressure setting.

② Start from the pressure that is considered adequate for each patient based on the various parameters.

③ Start from a certain fixed pressure (such as 12 cmH_2O).

④ Start from the low pressure setting and gradually increase it while monitoring the symptoms to find the optimal pressure setting.

In a prospective, double-blind study using a Codman-Hakim programmable-pressure valve (CHPV, Integra), the subjects were divided into a group in which the valve pressure was started at 20 cmH_2O and decreased gradually by 4 cmH_2O each month, and another group in which the pressure was fixed at 12 cmH_2O. The clinical symptoms were then

evaluated after 6 months.[262,263] There were no differences in efficacy between the two groups, and no further improvement was observed even when the pressure was reduced to below 12 cmH_2O.

Therefore, initially setting the pressure at 12 cmH_2O is adequate. However, in the fixed-pressure valve group, nine patients exhibited over-drainage (9/34), four of which dropped out in the latter half of the study. In another study that used the Strata valve (Medtronic, Minneapolis, MN, USA), comparison was also made between a group in which the valve pressure was fixed at performance level (PL) 1.0, and another group in which the pressure was started at PL 2.5 and gradually decreased until symptoms improved or over-drainage symptoms appeared. It was reported that over-drainage complications were more common in the former group.[239]

In minimizing the incidence of over-drainage, the initial pressure setting method ① is superior. However, adjustment from the high pressure setting requires multiple changes to the optimal pressure setting and takes time. Additionally, although the level of improvement was the same between the two groups with no significant difference, it should be noted that there seemed to be a delay in symptom improvement. For method ②, various CSF dynamic tests such as Rout and a method for estimating the set pressure based on ICP have been reported.[264–266] On the other hand, using the quantitative initial pressure setting method in a sitting position,[267] a quick reference table shows that for estimating the initial pressure based on height and weight (Table 4), both the number of changes and the range of the setting change are smaller than those of the methods described above.[268–270] This method, which is based on a sitting position with a large siphon effect, inevitably results in a higher setting. The initial pressure setting according to the quick reference table was adapted in the SINPHONI study for the patients treated with VP shunt surgery using CHPV[4] and in SINPHONI-2 study for the patients treated with LP shunt surgery using CHPV plus siphon-guard.[7] The usefulness and safety of the initial pressure setting were confirmed in these studies.

Prognosis after shunt surgery

CQ-14. What are the short-term and long-term outcomes of iNPH, and what degree of improvement can be expected for each symptom?

Symptoms usually improve after surgical intervention. However, the short-term outcomes are affected by postoperative complication, disease duration, severity of disease, tap test response, and typical imaging findings of DESH. The long-term outcomes are affected by the presence of any comorbidity. The degree of improvement in gait disturbance is the highest, followed by cognitive impairment and urinary dysfunction.

Recommendation Grade 2, Level of Evidence C

Outcomes after surgical treatment have been reported for varying periods, from 3 months to 6 years.[4,7,271–274] Based on evaluations such as mRS, improvement rate after shunt intervention is reported to be approximately 39–81% in 3–6 months,[7,271,272] 63–84% in 1 year,[4,7,273] 69% in 2 years,[274] and approximately 60–74% in 3–6 years.[275] However, in these studies, some of the subjects did not meet the diagnostic criteria stipulated in the Japanese and international guidelines, and sNPH patients may have been included.

Regarding the rate of improvement in symptoms after shunt interventions, gait disturbance showed the highest rate of improvement, and although the evaluation methods varied, it is reported to be approximately 60–77%.[273,276,277] Even for cognitive impairment, the evaluation methods varied; however, the improvement rate is reported to be 61–69%.[274,277,278] Regarding urinary incontinence, an improvement rate of 52% has been reported.[276] Although shunt interventions have been recognized to have a certain beneficial effect, the extent of their stated effectiveness varies. Moreover, the diagnosis of iNPH, modality of shunt intervention, symptom evaluation method, and criteria for assessing improvement can notably differ depending on the study. Short-term outcomes (at 1 year after shunt interventions) may be affected by complications related to the surgical procedure. Furthermore, results are also affected by the duration and severity of disease, response to tap test, and the status of typical imaging findings (DESH).[180,183,279]

The long-term outcomes are more affected by comorbidities. For example, stroke affects functional prognosis, cancer affects life prognosis, Alzheimer's disease affects cognitive function, and Parkinson's disease affects motor function.[208,274,280] All of these can notably affect the long-term outcomes of a shunt intervention. It is therefore good to predict the coexistence of comorbidities, such as Alzheimer's disease, using biomarkers before surgery.[272,274,280] Moreover, if the outcome can be predicted clinically using the frailty index or the comorbidity index, this can be useful for deciding which surgical modality will result in good postsurgical outcome.[281,282] If the Kiefer comorbidity index is 3 points or less, improvement rate following a shunt intervention is 93% after 2 years. If it is more than 4 points,

Table 4 Revised quick reference table for initial pressure setting of programmable differential pressure valve

Women	BW (kg)															
Ht (cm)	35	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110
140	16	12	9	6	3											
145	19	16	13	10	7	4										
150	23	19	16	13	10	7	4									
155	26	23	20	17	14	12	9	6	3							
160	29	27	24	21	18	16	13	11	8	5	3					
165	33	30	27	24	21	18	16	14	12	10	8	5	1			
170	36	34	31	28	25	23	20	18	15	13	11	9	6	4		
175	39	37	34	31	29	27	24	20	18	16	14	12	10	8	5	3
180	42	40	37	35	33	31	28	26	23	20	18	16	14	12	10	8

Men	BW (kg)															
Ht (cm)	35	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110
145	20	18	15	12	9	6	3									
150	23	20	18	15	12	9	6									
155	26	23	21	19	16	14	11	8	5	3						
160	29	27	24	21	19	17	14	12	9	6	4	1				
165	32	30	27	24	22	20	18	16	14	11	8	6	4	1		
170	35	33	31	28	25	23	21	19	16	14	12	10	7	5	2	
175	38	36	34	31	29	27	25	23	21	18	16	14	12	10	7	5
180	41	39	37	34	32	30	28	25	23	21	19	17	15	13	11	9

All quick reference table values are shown in cmH_2O.BW: body weight, Ht: height. (Revised from ref. 270).

the improvement rate is low, and no improvement can be expected if it is 6 points or more.[281] However, this index does not include cognitive impairment, such as Alzheimer's disease, which is a major component of iNPH comorbidity.

Evaluations of gait disturbance, cognitive impairment, and urinary dysfunction after shunt interventions have been performed using various scales that were either specific or not specific (e.g., mRS) to iNPH. Therefore, it is difficult to compare studies using various scales, and the development of a simpler, common evaluation method that can sensitively detect the effects of shunt interventions is awaited. For the time being, it will be better to evaluate the application of iNPHGS instead of assessing only the degree of independence with mRS.

Shunt surgery cost-effectiveness

CQ-15. Is shunt placement for iNPH effective from a healthcare cost-effectiveness perspective?

Shunt intervention for iNPH is medically and economically effective.

Recommendation Grade 2, Level of Evidence B

iNPH is a syndrome that causes gait disturbance, dementia, and urinary incontinence that can be improved with standard CSF shunt intervention; that is, iNPH is a treatable disease. Therefore, several studies have been conducted on shunt interventions from the viewpoint of medical economics.[283–286]

The economic effects based on the results of the SINPHONI and SINPHONI-2 studies reported that the incremental cost-effectiveness ratio 1 year after shunt intervention was 29934–40742 USD/quality-adjusted life year (QALY) for the VP shunt, and 58346–80392 USD/QALY for the LP shunt.[285] Moreover, the cost (sum of surgical cost and nursing care cost) of iNPH treatments was estimated to reduce 18 months after VP shunt surgery and 21 months after LP shunt surgery, compared to the cost of nursing care in untreated iNPH patients. The economic effects of iNPH treatment were also studied with the Markov model based on data from 30 Swedish iNPH patients. The study reported that an additional lifetime of 2.2 years and 1.7 QALY was gained with treatment, with an additional cost of €13,000.[286]

Conclusion

Almost 15 years have passed since the first edition of the Japanese guidelines for iNPH management was published in 2004. In the meantime, the recognition of iNPH has significantly increased, and it is no exaggeration to say that the diagnosis and treatment of iNPH have entered a new phase. We hope that this third edition of the guidelines will further refine the diagnosis and treatment of iNPH, and help patients, their families, and healthcare professionals involved in treating the condition.

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Conflicts of Interest Disclosure

The committee paid for expenses such as meeting venues and transportation for attending the committee meetings. The committee did not pay an honorarium to the committee members or study collaborators for writing manuscripts or participating in meetings.

The present guidelines have been prepared based on appropriate conflict of interest (COI) management by the operating rules of the Japan Neurosurgical Society, the Japanese Society of Neurology, the Japanese Society of Psychiatry and Neurology, and the Japan Radiological Society. The committee members, study collaborators, and evaluation/ coordinating committee members involved in these guidelines submitted self-reports to their respective academic societies regarding their COIs for the past 3 years based on the standards set by the academic societies to which they belong.

Honorarium for executives, stocks, patent royalties, lecture fees, manuscript fees, research expenses, subsidies, travel expenses, gifts, scholarships (encouragements) endowment, affiliation with an endowed chair.

Moreover, all organizations such as corporations targeted for the declaration are all "corporations/ corporate organizations related to medical research and organizations for profit-making purposes." After being reviewed by the COI Review Committee, the Guidelines were prepared/revised according to the results of the review.

The companies declared in the COI are shown below:

Actelion Pharmaceuticals Japan Ltd., Idorsia Pharmaceuticals Japan Ltd., Eisai Co., Ltd., Kaneka Medix Corporation, Software Service, Inc., Terumo Corporation, Sumitomo Dainippon Pharma, Mitsubishi Tanabe Pharma, Stryker Japan, Nippontectsystems co., Ltd., Nihon Medi-Physics Co., Ltd., Medtronic Japan Co., Ltd., Hitachi, Ltd., Fujitsu Limited, FUJIFILM Corporation, Heptares Therapeutics Ltd., Integra Japan, Mentis Cura Japan, PMOD Inc.

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